Update on the New Classification of Hepatic Adenomas

Clinical, Molecular, and Pathologic Characteristics

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• ***Context.***—**Hepatic adenoma is an uncommon, benign, hepatic neoplasm that typically occurs in women of child-bearing age, often with a history of long-term use of oral contraceptive drugs. This is usually detected as an incidental mass lesion in a noncirrhotic liver during imaging studies. Pathologic evaluation by needle core biopsy remains the gold standard for diagnosis. Molecular studies have revealed that hepatic adenomas involve unique molecular pathways that are distinct from hepatocellular carcinoma. Based on these studies, a French collaborative group has recently proposed a molecular-pathologic classification for hepatic adenomas. In addition, advances in molecular studies have led to reclassification of the "telangiectatic variant of focal nodular hyperplasia" as "hepatic adenoma, inflammatory subtype."**

Objective.—**To review the proposed, new classification of hepatic adenoma and the changes in diagnostic workup in light of the above-mentioned developments.**

Data sources.—**Review of published literature and illustrations from clinical case material.**

Conclusions.—**Definitive diagnosis of liver mass lesion on needle core biopsies has a decisive role in clinical management. With the advent of the new classification of hepatic adenomas and its prognostic implications, it is vital for pathologists to be aware of the morphologic features seen in different subtypes and the available diagnostic tools, such as immunohistochemistry, to help identify the correct subtype.**

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Hepatic adenoma (HA) is an uncommon, benign neoplasm of the liver, with hemangioma and focal nodular hyperplasia (FNH) being more frequent lesions. Traditionally, HAs have been seen in young women of child-bearing age who have a long history of estrogen-based, oral contraceptive steroid (OCS) use. Rarely, HAs have been reported in men. Before the advent of oral contraceptives, HAs were regarded as extremely rare, benign neoplasms. Incidental detection of HAs was due to increased use of imaging modalities for nonhepatic indications, which also contributed to the increased incidence. In women using oral contraceptives, the estimated annual incidence is 3 to 4 per 100 000 per year in North America and Europe.[1,2] The female predominance for HAs has not been observed in Asian women, which has been attributed to lesser use of oral contraceptives in Asian countries than in Europe and North America.[3,4]

Usually, HA lesions are solitary and asymptomatic. The presence of multiple nodules, typically having more than 10 nodules in the liver, indicates a unique entity called *hepatic adenomatosis*.[5] Large tumors can become symptomatic if they rupture or bleed spontaneously, leading to hemorrhagic shock.[6] Besides the risk of rupture and bleeding, a small subset of HA tumors have the potential to undergo malignant transformation.[7] Hence, it is important to diagnose and treat HA lesions.

Diagnosis of HA is usually made on needle core biopsies obtained for diagnostic workup of a liver mass. This can sometimes be a challenge for the pathologist, particularly when these lesions show overlapping morphologic features with FNH or well-differentiated hepatocellular carcinoma (HCC). Recent advances in the understanding of the molecular-genetic pathways of oncogenesis have shown that HAs are monoclonal neoplasms with unique molecular signatures that involve oncogenetic pathways that are distinct from HCCs. Based on this information, in 2006, a French collaborative group proposed a molecular-pathologic classification for HA.[8] That classification divides HA into 4 groups, primarily based on the molecular characteristics, as determined by immunohistochemical markers and their correlation with histologic features. These 4 subtypes are (1) HAs with inactivating mutations of hepatocyte nuclear factor 1α (*HNF1A*; HA-H), (2) HAs with activating mutations of β-catenin gene (HA-B), (3) HAs without mutations of the *HNF1A* or β-catenin genes and with inflammatory features (HA-I), and (4) unclassified HAs that have no specific gene mutations or unique morphologic features (HA-U).[8] This classification is clinically relevant because it identifies a subset of HAs, specifically HA-B, with increased potential for malignant transformation.[7] Furthermore, it helps in identifying cases for which genetic counseling is recommended, ie, in the subset of patients

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with hepatic adenomatosis that shows a steatotic morphology.[9] Hepatic adenomas with steatosis in hepatic adenomatosis resemble *HNF1A*-mutated adenomas, which are morphologically distinct because of presence of steatosis. A familial form of hepatic adenomatosis involves germline mutations of *HNF1A* and is associated with maturity-onset diabetes mellitus of youth, type 3 (MODY3).[5] The rationale for genetic counseling is to search for germline mutations of the *HNF1A* in family members of patients of hepatic adenomatosis to identify familial predisposition for the disease.[8] From a histopathologic perspective, the classification is simple, reproducible, and easy to analyze because it is based on the use of immunohistochemistry for subtyping. Thus, there has been a paradigm shift in the diagnostic workup of HAs to classify them based on the categories mentioned above. Recent reclassification of *telangiectatic FNH* as *inflammatory hepatic adenoma*, based on molecular genetics and proteomic profiling, has added to the morphologic and molecular heterogeneity of HAs.[10]

PATHOGENESIS AND RISK FACTORS

In 1973, Baum et al[11] first suggested the causal association for HAs with intake of OCS. Subsequently, a striking increase in the incidence of HA was observed because of increased OCS use. In 1979, Rooks et al[2] reported that the occurrence was related to dose and duration of OCS use. Increasing duration of OCS use increases the risk of HA.[2] Since then, there has been, to our knowledge, no systematic study on the epidemiology of HAs, but they are thought to be less common with the use of modern oral contraceptives, which contain less estrogen.[12] Regression of HA has been observed with the termination of OCS use.[13] Of the HA subtypes, HA-H and HA-I occur more commonly in women with a history of OCS use. In men, the occurrence of HA is associated with the use of anabolic-androgenic steroids.[14] The HA-B subtype occurs more frequently in men. Hepatic adenomas can also occur following androgenic steroid therapy for Fanconi anemia and in patients with elevated levels of endogenously produced androgens and sex hormone imbalance.[15,16] Other causal associations include types I and III glycogen storage disease,[17] Klinefelter syndrome,[18] familial adenomatosis polyposis,[19] and obesity.[20] The HA-I subtype has been reported to be associated with high body mass index,[21] alcohol consumption,[22] glycogen storage disease type 1,[23] and primary sclerosing cholangitis.[24] Typically, HA is a neoplasm of noncirrhotic liver; however, a recent, small series[25] of hepatocellular neoplasms occurring in cirrhotic livers secondary to alcohol consumption has been reported from Japan. Those neoplasms have morphologic characteristics similar to HA-I and show diffuse expression of serum amyloid-A (SAA).[25] A recent case[26] of HA was observed in a *Hepatitis B virus*–associated cirrhotic liver as well.

The familial form of liver adenomatosis involves a germline mutation of the *HNF1A* gene and is associated with MODY3.[5] Thus, the clinical behavior of liver adenomatosis is similar to that of HA-H. Although HA is a benign, monoclonal neoplasm, there is a small, but definite, risk of malignant transformation.

MOLECULAR/GENETIC BIOLOGY

In 2002, Bluteau et al[27] first described the inactivation of transcription factor 1 (*TCF1*) gene as an early event in the oncogenesis of HA. Since then, tremendous advances in basic research have led to major breakthroughs in our understanding of HA oncogenesis at the molecular level. Recurrent mutations involving the *TCF1* gene (encoding for protein *HNF1A*), *CTNNB1* gene (encoding for β-catenin), and *gp130* gene have been described in HAs.[27–29]

TCF1 (also known as *HNF1A*) Gene

TCF1 is a tumor suppressor gene involved in liver tumorigenesis. It is located on the long arm of chromosome 12, encoded by 10 exons, spanning 23 kilobases, and is expressed in various tissues, including liver, kidney, pancreas, and digestive tract. It encodes a transcription factor HNF1, which, in the liver, is implicated in hepatocyte differentiation and is required for expression of certain liver-specific genes, including albumin, β-fibrinogen, and α_1-antitrypsin.[30] Bluteau et al[27] reported that the recurrent loss of heterozygosity at 12q24 or somatic mutations of the *TCF1* gene led to biallelic-inactivating alterations, which is an important oncogenetic event in HA. The French Bordeaux group showed that HAs with bi-allelic inactivating mutations in *TCF1* (*HNF1A*) gene constituted a homogenous, morphologically distinct, group that comprise 35–40% of all HAs, and classified the group as "*HNF1A* mutated hepatic adenomas (HA-H)."[8] This subtype constituted a lower percentage (15%–18%) of all HAs in the Japanese population.[4]

In most (about 85%) of this subtype of HAs, mutations are somatic in origin; however, in a few cases, one mutation is somatic, and the other is germline in origin. Jannot et al[31] reported the heterozygous germline-inactivating mutations of the *CYP1B1* gene might increase the incidence of HA in women with *TCF1* (*HNF1A*) gene mutations. Furthermore, heterozygous germline mutations in the *TCF1* gene have been associated with occurrence of a rare autosomal-dominant condition (MODY3), which presents in early adulthood (usually younger than 25 years).[5] The *TCF1* gene mutation in these patients affect only one allele and lead to a primary defect in insulin secretion by the pancreatic β cells. Biallelic inactivation of the *TCF1* gene in patients with MODY3 confers a predisposition to develop familial liver adenomatosis.[32] *HNF1A* mutation increases lipogenesis by promotion of fatty acid synthesis and down-regulation of liver-type fatty acid binding protein 1 (L-FABP), leading to diffuse intralesional steatosis.[30]

β-Catenin Gene (also known as CTNNB1)

β-catenin is a component gene of Wnt/β-catenin pathway, which is important in hepatocellular development and physiology. In normal hepatocytes, activation of the β-catenin gene is transient, followed by rapid degradation of the β-catenin protein, which is facilitated by a set of genes, including axins, glycogen *S*-kinase 3 (*GSK3*), and adenomatosis polyposis coli (*APC*). Decreased degradation, sustained activation, and nuclear accumulation of β-catenin protein could be due to either a mutation of the β-catenin gene or mutations in the axin, *APC*, or *GSK3* genes. Mutated β-catenin protein has a prolonged half-life and is resistant to degradation. In 2002, Chen et al,[28] from Taiwan, reported interstitial deletions of the β-catenin gene in 3 of the 10 hepatic adenomas (30%) in their study. Similarly, Rebouissou et al,[33] of the Bordeaux group, reported activating β-catenin mutations in 15% to 19% of cases. Mutations in other genes of the Wnt pathways, such as axins or *APC*, have not been observed in sporadic HA. However, in patients with familial polyposis coli, germline biallelic

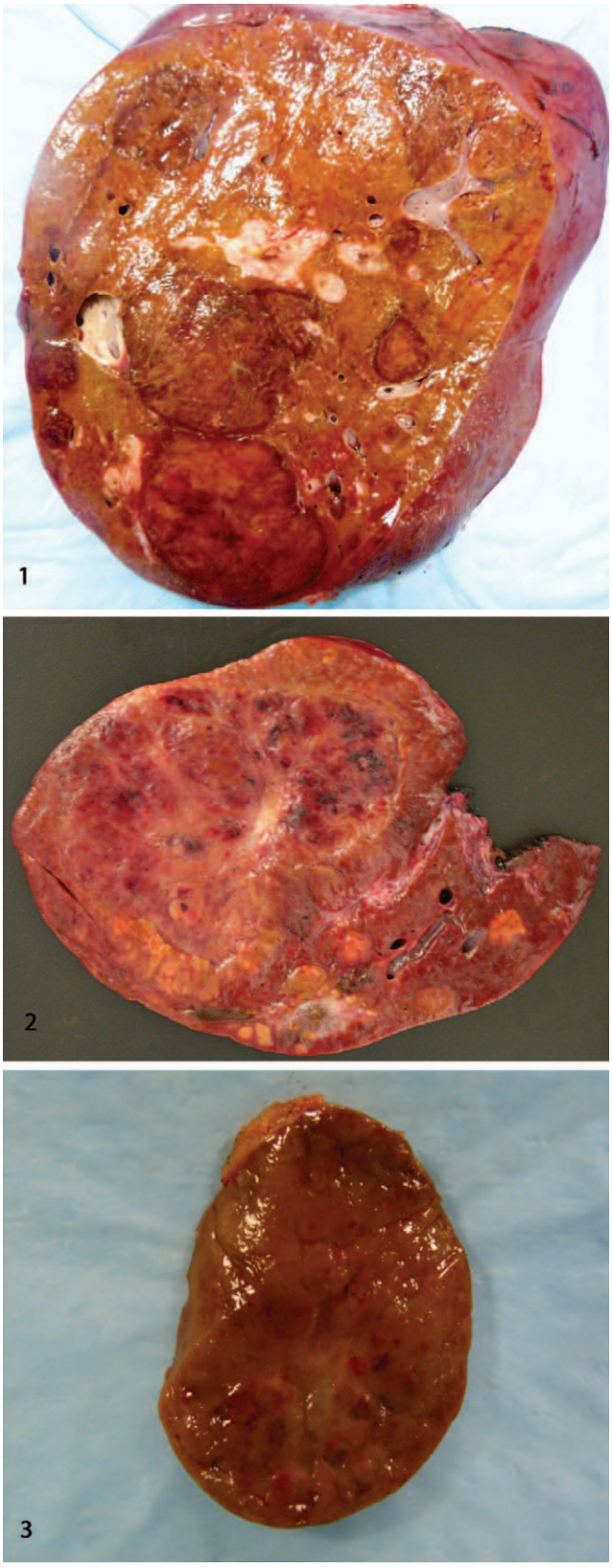

Figure 1. *Right lobectomy specimen with liver adenomatosis. Multiple variably sized nodules are present in a background of an unremarkable liver parenchyma. Twelve nodules were present in the specimen. Note that each nodule has a hemorrhagic rim.*

mutations of the *APC* gene caused increased susceptibility to development of HA because of accumulation and constitutive activation of β-catenin.[34] Mutations of β-catenin have also been seen in 20% to 34% of well-differentiated HCCs.[35] The HA-B subtype is more frequently associated with malignant transformation.[35]

GP130 Gene

Some HAs show sustained activation of interleukin 6 (IL-6) receptor signaling because of somatic gain of function mutations of the IL-6 signal transducer gene (*IL6ST* gene), which encodes for glycoprotein-130 (*gp130*); *gp130* is a component of the IL-6 receptor.[29] This activation of IL-6 promotes the signal transducer and activation of transcription 3 (*STAT3*) signaling pathway and induces an acute-phase inflammatory response within neoplastic hepatocytes. This is manifested as overexpression of acute-phase reactants, such as SAA and C-reactive protein (CRP), and inflammatory cell infiltration of the tumor. Such HAs are referred to as *inflammatory HA* (HA-I) and comprise 30% to 35% of all HAs.[35] Somatic mutations of the *IL6ST* gene are seen in about 60% of the HA-I subtype. Nonmutated HA-I shows similar expression profiles for *STAT3* activation and gp130 protein expression, but the mechanisms for that expression are not clear.[29] About 10% of the HA-I cases show coexistent β-catenin mutations. Historically, the HA-I subtype was referred to as *telangiectatic focal nodular hyperplasia* and was thought to belong to the FNH family. In 2004, Paradis et al,[36] and in 2005, Bioulac-Sage et al,[10] showed that telangiectatic focal nodular hyperplasias are monoclonal neoplasms that are morphologically and biologically closer to HAs and are distinct from typical FNHs. Based on those observations, telangiectatic focal nodular hyperplasia is included within the subgroup HA-I in the new classification schema.

CLINICAL FEATURES

Hepatic adenomas occur almost exclusively in woman of child-bearing age. Hepatic adenoma clinical presentation varies. Usually, they are asymptomatic, with normal liver function test results and no elevation in serum tumor markers, such as α-fetoprotein. They may be discovered incidentally during diagnostic imaging, such as multiphasic magnetic resonance imaging (MRI) or computed tomography (CT), during diagnostic studies for unrelated reasons. A few HAs are complicated by rupture and spontaneous bleeding, leading to intratumoral and intraperitoneal bleeding. The risk of rupture is increased in patients with tumor larger than 7 cm and associated oral contraceptive use.[6] Those patients present with abdominal pain, elevated liver enzymes, and hypovolemic shock. The HA-I subset may present with signs of chronic anemia or "systemic inflammatory syndrome," which includes fever, leukocytosis, abnormal liver function test results, and elevated levels

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Figure 2. *Gross appearance of a large hepatic adenoma and multiple smaller adenomas. The cut surface of the largest tumor has a variegated appearance representing areas of necrosis, whereas the smaller nodules are tan and homogeneous.*

Figure 3. *A resection specimen of a hepatic adenoma, inflammatory type (HA-I) that was completely enucleated. The cut surface demonstrates alternating pale and dark-red foci, typical for the HA-I subtype.*

Hepatic Adenoma Subtypes, Frequencies, Molecular Findings, Pathologic Features, and Immunohistochemistry				
HA Subtype	Frequency Range, %	Molecular Findings	Pathologic Features	Immunohistochemistry
HA-H	35–40	Somatic mutations of (85%) *TCF1* (*HNF1A*) gene; heterozygous germline mutations (<5%) of *CYP1B1* gene	Steatosis, lack of inflammation, and cytologic atypia	Decreased or absent L-FABP in neoplastic hepatocytes, compared with nonneoplastic liver; patchy CD34 expression; focal, interspersed CK7 positivity in small hepatocytes
HA-B	15–19	β-catenin gene–activating mutations	Pseudoacinar pattern, cytologic atypia, steatosis, and/or lack of inflammation	Increased nuclear β-catenin protein expression; strong diffuse glutamine synthetase positivity
HA-I	30–35	Gain-of-function mutations of the *IL6ST* gene; 10% with coexisting β-catenin gene mutations	Pseudoportal tracts with thick-walled arteries and lack of bile ducts or veins; inflammatory infiltrate; ductular reaction; sinusoidal dilatation; and peliosis	Diffuse, strong serum amyloid-A and C-reactive protein expression; CD34 reactivity around pseudoportal tracts; diffuse glutamine synthetase positivity if associated with β-catenin mutation
HA-U	10	No specific mutations	No distinctive morphology	No specific protein expression

Abbreviations: HA-B, β-catenin–mutated hepatic adenoma; HA-H, *HNF1A*-mutated hepatic adenoma; HA-I, inflammatory hepatic adenoma; HA-U, hepatic adenoma, not otherwise specified; L-FABP, liver-type fatty acid binding protein expression.

of acute-phase reactants, such as CRP and SAA.[9] Malignant transformation is an uncommon, but well-recognized, complication of HA. The risk of malignant transformation varies with the subtype of HA and is highest in the HA-B subtype.[8]

Hepatic adenomas are usually solitary; however, multiple adenomas (range, 2–9) are described with prolonged use of OCS, type I glycogen storage disease, and obesity.[20] *Liver adenomatosis*, first described by Flejou et al[37] in 1985, is considered an entity distinct from HA and shows multiple HAs (usually >10) in a background of normal liver (Figure 1). The sporadic form of liver adenomatosis occurs predominantly in women in their third or fourth decades and is also associated with prolonged OCS use.

PATHOLOGY

Gross Pathology

The typical gross appearance of HA is a solitary or multiple, unencapsulated, and well-demarcated mass lesion (Figure 2), which can occasionally be pedunculated or encapsulated. Among the HA subtypes, the HA-H, and HA-I cases may form multiple masses. The mass has a soft and fleshy consistency, and the size ranges from 1 to 30 cm.[38] The cut surface may be solid tan or yellow, depending on the presence or absence of steatosis. Intratumoral hemorrhage can give rise to a soft, necrotic, red-brown lesion. Some tumors show fibrotic foci with brown discoloration, representing old intratumoral hemorrhage. The HA-I subtype shows alternating pale-red and dark-red areas (Figure 3). Spontaneous rupture of the tumor can also cause a subcapsular hematoma. The background liver is typically noncirrhotic.

Histopathology and Immunohistochemistry

Typically, HA microscopic features show benign hepatocytes arranged in mildly thickened cell plates, with a preserved reticulin network and thin-walled arteries. The arteries and arterioles are not accompanied by other portal tract elements, such as bile ducts, portal veins, or fibroconnective tissue. Other variable features include the presence of steatosis, inflammatory cell infiltrates, dystrophic blood vessels, ductular reaction, sinusoidal dilatation, hemorrhage, and peliosis. Rare cases containing Dubin-Johnson–like pigment have been reported.[39] As mentioned, 4 subtypes of HA have been proposed based on their molecular and histologic features (Table). The distinctive features of each subtype are discussed below.

HA-H Subtype.—In addition to the typical features of HA, the HA-H subtype characteristically presents with steatosis and an absence of inflammatory infiltrate or cytologic atypia[8,35] (Figure 4, a). The steatosis sets this subtype apart from the other HA subtypes, and only rare cases of HA-H show the absence of steatosis. Usually, the amount of steatosis is of moderate to severe degree but often spares the arterialized zones.[40] The reticulin framework is preserved. The tumor cells lack immunoexpression of L-FABP because it is down-regulated in HA-H.[40] The nonneoplastic hepatocytes surrounding the mass lesion show normal expression of L-FABP and serve as positive controls for the immunostain. That immunostaining pattern also delineates the boundaries of the tumor (Figure 4, b). Patchy CD34 immunostaining is observed in the arterialized areas and is indicative of sinusoidal capillarization. Immunostaining for CK7 shows dispersed, small hepatocytes that resemble stem cells and intermediate hepatobiliary cells. The neoplastic hepatocytes are negative for inflammatory proteins, such as SAA and CRP and are also negative for glutamine synthetase by immunohistochemistry.

HA-B Subtype.—The HA-B subtype is morphologically characterized by pseudoacinar formation and mild cytologic atypia, in addition to typical features of HA. Steatosis is rare, and inflammation is absent. Tumors with this morphology are difficult to distinguish from well-differentiated HCC and can be misdiagnosed as HCC. Immunostaining with β-catenin shows a heterogenous pattern of nuclear and cytoplasmic reactivity (Figure 5, a). Aberrant nuclear staining of β-catenin is a distinct feature of this HA subtype. In addition, the tumor has diffuse and strong cytoplasmic glutamine synthetase reactivity (Figure 5, b). Glutamine synthetase is an enzyme that is involved in nitrogen metabolism and is upregulated in HA-B because of

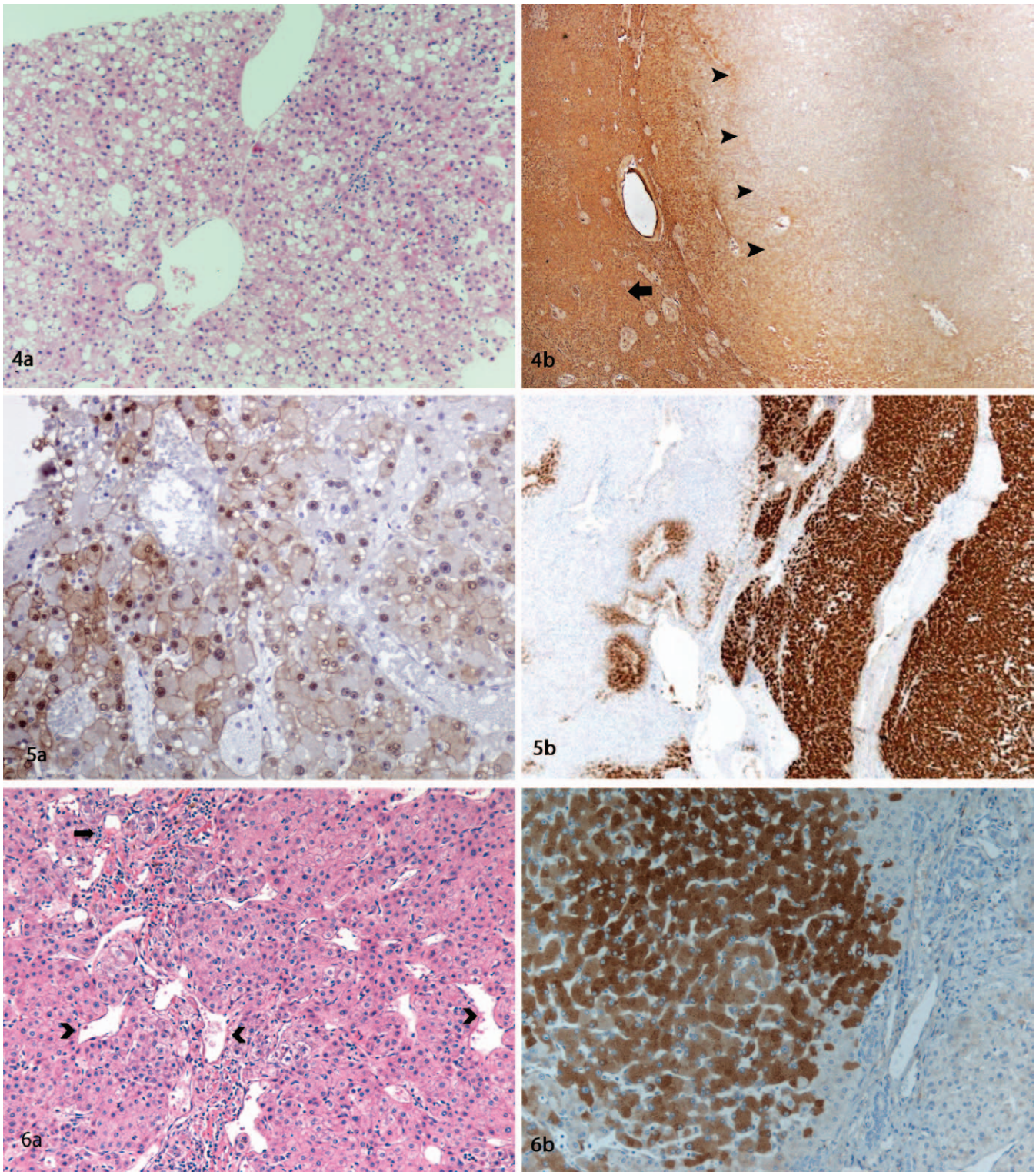

Figure 4. *a, Liver needle biopsy. Microscopic appearance of* HNF1A*-inactivated hepatic adenoma (HA-H) with variable amounts of steatosis. b, Microscopic appearance of HA-H at low magnification demonstrating lack of immunoexpression of liver-type fatty acid binding protein (L-FABP) (arrowheads). In contrast, the expression is preserved in the cytoplasm of adjacent nonneoplastic hepatocytes (arrow) (hematoxylin-eosin, original magnification ×200 [a]; immunoperoxidase, original magnification ×40 [b]).*

Figure 5. *a, Immunostaining for activating mutations β-catenin in a hepatic adenoma (subtype HA-B), showing aberrant staining in the nuclei of tumor cells, which is indicative of β-catenin mutation. b, Diffuse and strong immunoexpression of glutamine synthetase in β-catenin–activated hepatic adenoma (HA-B). Note the lack of expression in the nontumoral liver (immunoperoxidase, original magnifications ×200 [a and b]).*

Figure 6. *a, Typical histology of inflammatory hepatic adenoma (HA-I) with prominent sinusoidal dilatation (telangiectasias) (arrow heads) and the presence of pseudoportal tracts (arrow) containing a mild, chronic inflammatory infiltrate. b, An HA-I with diffuse cytoplasmic immunoexpression of the C-reactive protein. The nonneoplastic hepatocytes at the periphery show lack of immunoexpression (hematoxylin-eosin, original magnification ×200 [a]; immunoperoxidase, original magnification ×100 [b]).*

activation of *GLUL*, which is a β-catenin target gene that codes for glutamine synthetase. Glutamine synthetase staining results are negative in other HAs.

HA-I Subtype.—This subtype characteristically shows pseudoportal tracts that lack veins and bile ducts and contain large, thick-walled arteries surrounded by fibroconnective tissue with variable ductular reaction and inflammation (Figure 6, a). There is multifocal, sinusoidal dilatation and peliosis. Focal steatosis may be present. The inflammation is usually patchy and is predominantly mononuclear, comprising lymphocytes and histiocytes admixed with a few neutrophils and plasma cells.[41] The neoplastic hepatocytes show strong and diffuse immunoreactivity of acute-phase inflammatory reactants SAA and CRP (Figure 6, b). The positive immunostaining demarcates the tumor from the surrounding nonneoplastic liver. Cytokeratin 7 immunostain highlights the ductular reaction, and CD34 immunostain is positive around the pseudoportal tracts. α-Smooth muscle actin highlights the thick arteries and activated hepatic stellate cells along the sinusoids. The L-FABP test results are positive both within the tumor and in the surrounding liver parenchyma. Glutamine synthetase staining is usually negative; however, some cases show patchy, centrilobular staining. About 10% of HA-I cases are β-catenin activated and show aberrant nuclear β-catenin expression along with diffuse expression of glutamine synthetase. [39] The nonneoplastic liver has also been reported to show small foci of morphologic changes, such as mild/moderate steatosis, unaccompanied arteries, sinusoidal dilatation, and expression of CRP.[42]

HA-U Subtype.—This category has been created to include HAs that show adenoma-like morphology but lack distinctive morphologic and molecular (immunophenotypical) features of the different subtypes described above and cannot, therefore, be classified into any of those groups. Some HAs show near-total necrosis or hemorrhage making it difficult to characterize them; thus, they are included in this category.[25] Overall, these tumors constitute 5% to 10% of HAs. It is important to rule out a well-differentiated HCC among this group of tumors.[40]

Differential Diagnosis

The 3 main differential diagnoses include (1) FNH, (2) well-differentiated HCC, and (3) nonneoplastic liver with multifocal steatosis. The 2 primary hepatic mass lesions that show a morphologic overlap with HA are FNH and well-differentiated HCC. At times, nonneoplastic liver with multifocal steatosis may mimic HA morphologically with *HNF1A* mutations.

Focal Nodular Hyperplasia.—Focal nodular hyperplasia is a nonneoplastic, polyclonal lesion that manifests as a hyperplastic response of hepatocytes secondary to abnormalities in blood flow.[42] Morphologically, it is characterized by a nodular architecture; central scarring; ductular reaction; aberrant, thick-walled blood vessels; telangiectasias: and an absence of interlobular bile ducts. As mentioned earlier, a subset of FNH with prominent telangiectasias (sinusoidal dilatation), previously referred to as *telangiectatic FNH*, has been shown to be monoclonal by molecular studies and is now reclassified as *HA-I* by the World Health Organization.[43,44]

Special Stains and Immunohistochemistry to Aid in the Differential Diagnosis.—The 2 entities—HA and FNH—are best distinguished with the help of immunohistochemical stains for glutamine synthetase and inflammatory proteins, such as SAA or CRP.[45,46] Focal nodular hyperplasia shows a characteristic "maplike" pattern of cytoplasmic glutamine synthetase immunostaining with large, anastomosing cords of hepatocytes that express glutamine synthetase, and are usually focused around the hepatic veins with hepatocytes close to fibrotic bands often spared. These lesions do not express cytoplasmic inflammatory proteins SAA or CRP. In contrast, the HA-I subtype is negative for glutamine synthetase immunostaining, or it may show only focal, centrizonal positivity that is typically diffusely positive for inflammatory proteins SAA and CRP, with cytoplasmic immunoexpression.[46]

Well-Differentiated HCC.—Well-differentiated HCC is an important diagnostic differential for HA in needle biopsies from hepatic mass lesions. Histologic features in favor of HCC include thickened cell plates (often >4 cells thick), loss of the reticulin framework, cytologic atypia, mitotic figures, and pseudoacinar architecture. However, HA-B can show some of these features of cytologic and nuclear atypia. The distinction can be challenging.

Special Stains and Immunohistochemistry to Aid in the Differential Diagnosis.—Reticulin stains can sometimes be helpful because the reticulin framework is completely lost in well-differentiated HCC; therefore, its absence favors HCC. However, HAs show variable preservation of the reticulin framework with only patchy loss of staining, which can be difficult to interpret in core needle biopsies. In such situations, immunostaining with markers, such as glypican-3 and heat shock protein 70 (HSP70) can be helpful. Glypican-3 has a reported sensitivity of 40% to 50% and a specificity of 100% for well-differentiated HCC.[46,47] Similarly, HSP70 has a sensitivity of 46% and a specificity of 100% for well-differentiated HCC.[47] Thus, the positive immunoexpression of these 2 markers is useful in differentiating HA from well-differentiated HCC; however, negative staining is not helpful. Glutamine synthetase immunostaining is noncontributory because a certain proportion of both HA and HCC are positive for glutamine synthetase immunoexpression. Similarly, CD34, which is an immunomarker for endothelial cells, is observed to be positive in HCC because of the capillarization of sinusoids in HCC. However, HAs may also show patchy immunoexpression of CD34, thereby limiting the potential of CD34 to differentiate between the 2 entities.[46,47] Other immunohistochemical proteins, such as HepPar1, polyclonal carcinoembryonic antigen, and arginase 1, are markers of hepatocellular differentiation and would be positive in both benign or malignant hepatocellular lesions and so are not helpful in differentiating HA from HCC.[46]

In challenging cases in which the neoplasm expresses nuclear β-catenin, but the HSP70 or glypican-3 immunostains are negative, one has to consider the potential for HCC developing in HA-B. According to a recent study by Evason et al,[48] atypical hepatocellular nodules that occur in atypical settings (eg, in women who are older than 50 years and in men) and those with atypical morphologic features have a high rate of β-catenin staining. The authors suggest those tumors probably represent well-differentiated HCC. Based on that, we recommend patients with needle biopsy of mass lesions and any of these clinical scenarios be closely followed or resection be performed.

Nonneoplastic Liver With Steatosis.—Nonneoplastic liver with steatosis can, at times, be nodular and cause diagnostic confusion with liver adenomatosis, particularly on imaging studies, because of the presence of steatosis in

the 2 entities. Hence, a liver biopsy should be obtained for a definitive diagnosis. Morphologically, the 2 conditions can look similar because unaccompanied arteries can occasionally be seen in nonneoplastic liver with steatosis. In such circumstances, use of immunohistochemical stain for L-FABP may be helpful in differentiating the 2 entities.[35]

Radiologic Imaging Modalities

Imaging studies are an important part of the diagnostic workup of liver masses. Modern cross-sectional imaging relies on the presence of intralesional steatosis, necrosis, and hemorrhage to diagnose HA.[49] Hepatic adenomas are better characterized by multiphase helical CTs and MRIs than they are by "generic" ultrasonography, which has a sensitivity of about 30%.[50] Traditionally, HA was considered to have variable imaging characteristics and was described as a heterogeneous hypervascular mass with areas of fat, hemorrhage, and necrosis on multiphase CT or MRI.[51] With the introduction of the new phenotype-genotype classification of HA, the variable imaging characteristics correlated well with different groups described in the classification.[52] On multidetector CT/MRI imaging HA-I is hyperintense on T2-weighted image, corresponding to foci of sinusoidal dilatation and, on contrast enhanced imaging, show persistent arterial enhancement in both venous and delayed phases. The HA-H subtype characteristically shows diffuse steatosis readily characterized by MRI as diffuse signal dropout on out-of-phase T1-weighted imaging. On contrast-enhancement studies, HA-H shows arterial enhancement that does not persist into the venous phase. The reported sensitivity and specificity for detection of HA-I by imaging is 85.2% and 87.5%, and that of HA-H is 86.7% and 100%, respectively.[52] The HA-B mutation may appear as homogenous or heterogenous hypervascular masses and lack intratumoral fat, which are difficult to distinguish from HCC on imaging. The other major differential diagnoses include FNH. Gadolinium-enhanced MRI features of a homogenous, hypervascular lesion with a central scar has 70% sensitivity and 98% specificity for the diagnosis of FNH.[53] Liver biopsy remains the gold standard for diagnosis.

PROGNOSIS AND CURRENT TREATMENT

The overall frequency of malignant transformation is estimated to be 4.2% for all adenomas and 4.5% for resected adenomas.[7,38] Regression of HA upon cessation of OCS use does not abort the risk of malignant transformation in women.[54] High-risk groups for malignant transformation include patients with a history of androgenic or anabolic steroid intake, male patients, and patients with glycogen storage disease.[38] Farges et al,[55] in a recent study, reported an increasing frequency of malignant transformation in men (47%), as compared with women (4%), and attributed the malignant transformation to the associated metabolic syndrome in most men. They further proposed that the treatment of HA be gender specific. The HA-B subtype has been found to be more frequently associated with the development of HCC.[8,55] Evason et al[48] suggested a subset of hepatic neoplasms in noncirrhotic liver, which morphologically and immunohistochemically resemble HA-B and occur in unusual clinical settings, including in men, in women older than 50 years, and in girls younger than 15 years, may represent extremely well-differentiated HCCs. This observation was based on about one-half of such patients showing cytogenetic alterations similar to those seen in HCC.

The potential for malignant transformation and the risk of hemorrhage drives active surgical interventions in large HAs. Surveillance with imaging studies performed at regular intervals may be sufficient in tumors smaller than 5 cm.[56] Surgical resection is recommended for HAs larger than 5 cm, those with intratumoral hemorrhage, and those that increase in size.[56–58] Farges et al[55] suggested active surgical intervention in male patients with HAs, irrespective of tumor size. Newer and less-invasive techniques, such as radiofrequency ablation and transarterial embolization, are increasingly being used in the treatment of HAs.[56]

CONCLUSION

Needle core biopsy of the mass is the first-line approach for diagnosis of liver neoplasms. At times, differentiating hepatic adenomas from FNH and well-differentiated HCC can be challenging in such small samples. With the advent of the new classification of hepatic adenomas—a classification scheme based on morphologic features, immunohistochemical characteristics, and genetic molecular expression—pathologists must be able to identify the subtype to help guide the clinical management of patients with these tumors.

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